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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	**PAPER NUMBER**
1654	

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07/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,582	LICHA ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25,33 and 35-41* is/are pending in the application.

4a) Of the above claim(s) *2,3,5,8,11,14-17,20-25,33 and 36-39* is/are withdrawn from consideration.

5)☒ Claim(s) *6,7,9,10,12,13 and 40* is/are allowed.

6)☒ Claim(s) *1,4,18,19,35 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments/Arguments

Upon further consideration, the finality of the Office action mailed July 28, 2006 is withdrawn, necessitated by the new grounds of rejection set forth below. Accordingly, the Notice of Appeal is rendered moot.

Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 6, 7, 9, 10, 12, 13 and 40 remain allowed for the reasons of record.

Claims 2, 3, 5, 8, 11, 14-17, 20-25, 33 and 36-39 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 30, 2005.

Claims 1, 4, 18, 19, 35 and 41 have been examined on the merits.

With regards to the rejection under 35 USC § 103, the examiner has set forth a new argument below, and has addressed Applicant's arguments herein.

Applicant reasserts the arguments that (1) the fact pattern in *Jones* is analogous to the instant claims, (2) the examiner relies upon the instant disclosure as a roadmap, i.e. hindsight reasoning, and (3) because 8 references are relied upon, the *prima facie* case of obviousness is improper. Applicant further argues that (4) "Not one single reference generically teaches each and every component of the claimed invention herein and/or even how the pieces of the various compounds should be formulated into a single structure" (page 4), (5) Chorev would not be considered analogous art, and (6) there is no common core in the compounds of the relied

references. It is noted that while the examiner clearly set forth the rejection using Zaheer as the primary reference, Applicant has argued a different reference in the rebuttal.

Respectfully, the examiner disagrees. As stated previously, contrary to Applicant's arguments, *Jones* is not analogous to the instant rejection. *Jones* compares two compounds $HOCH_2CH_2NHCH_2CH_2OH$ and $NH_2CH_2CH_2OCH_2CH_2OH$, and the issue is connectivity of atoms within a single structure, and the non-obviousness to rearrange the atoms, and not the reliance upon secondary references to bring in the missing elements or how one could extrapolate molecular rearrangement of atoms to reliance upon multiple references under 35 USC § 103.

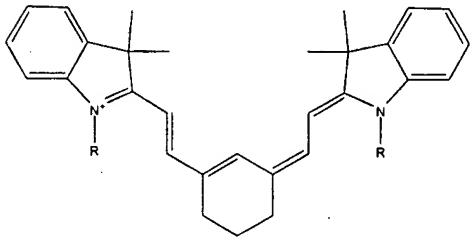
Additionally, it appears that Applicant is improperly requiring an anticipatory reference be provided by the examiner under 35 USC § 103, in as much as Applicant argues, "not one single reference even generically teaches each and every component of applicants' invention." Such a reference would be used under 35 USC § 102 in an anticipatory rejection.

Further, in response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, contrary to Applicant's opinion, the elements were not selected 'in isolation' or 'pieced together', and the examiner did not rely upon the instant disclosure. The art, as identified by the examiner, provided the

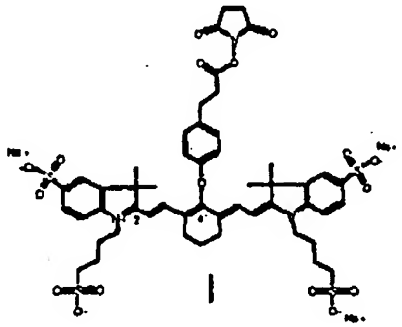
knowledge which was within the level of ordinary skill at the time of the invention, and thus set forth a proper *prima facie* case of obviousness.

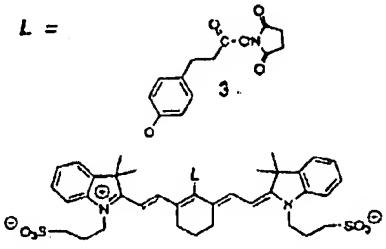
In response to Applicant's arguments that the compounds do not share a common core, the compounds relied upon, do indeed, share a common core as set forth by the examiner, which would be immediately recognized by one of skill in the art.

The compounds relied upon previously are depicted graphically to assist in visualizing the clear common core of two indole groups with a common linker having the core:

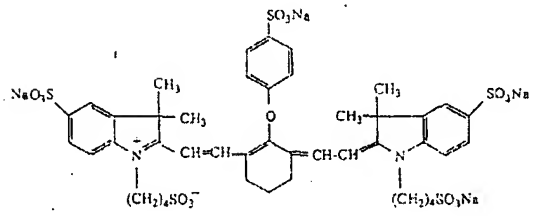


. The compounds having this core are:

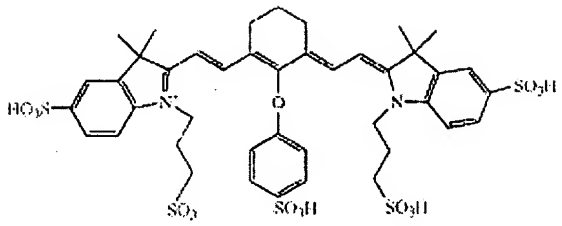
Zaheer: 

; Flanagan: 

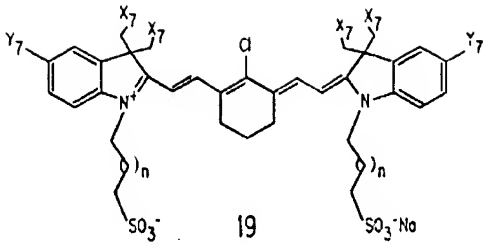
;

Miwa: 

; and Achilefu:



and



19

. Such compounds clearly share a significant common core, and Applicant's arguments that, "they have nothing in common other than that they are both compounds made up of various ations, e.g., carbon, nitrogen, etc." (page 5) is inaccurate with regards to these compounds. Additionally, if Applicant were comparing the core compounds (above) with the linker of Chorev, Applicant has misconstrued the examiner's arguments of core structure by extending it to the linkers.

Here, the compounds of the prior art are highly analogous, sharing a significant core structure, where any one reference could be relied upon as the primary reference. The motivation to form the instantly claimed compounds is derived from the references, to make a compound that is low in toxicity and selective towards sulfhydryl groups.

Furthermore, in response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Claim Objections

Claim 41 is objected to because of the following informalities: "solventmolecule" should recite "solvent molecule". Appropriate correction is required.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 41 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Applicant argues that it would not be an undue burden to make solvates of the compounds of the invention, asserting that, "there is no basis for the rejection" (page 6) because,

allegedly, "The Examiner has not established any basis to doubt objective enablement," and that, "There is no indication that one of ordinary skill in the art would have questioned that solvates could be formed in view of the disclosure and the state of the art" (page 6). Applicant further contends that making solvates is routine work and that any problems incurred could be determined through routine testing (page 7).

Respectfully, the examiner disagrees. Contrary to Applicant's assertion, the examiner clearly established a basis to doubt the "objective enablement", through the reference to Vipagunta, which clearly teaches that solvates of compounds cannot be predicted. Thus, there is ample reason to doubt the enablement, and when taken together with the lack of guidance and examples in the instant disclosure, one would clearly be burdened with undue experimentation to make solvates.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn generally to solvates of the compounds of the invention.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

VIPPAGUNTA (S.R. Vippagunta, et al. Adv. Drug Delivery Rev. (2001) 48, pages 3-26) teaches that, "The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition, but different internal crystal structures, and therefore, possess different physico-chemical properties." (page 4). "Solvates, also known as pseudopolymorphs, are crystalline solid adducts containing solvent molecules within the crystal structure, ... giving rise to unique differences in the physical and pharmaceutical properties of the drug. If the incorporated solvate is water, a solvate is termed a hydrate." (page 4).

Vippagunta teaches that, "Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties. such as density, hardness. tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules." (page 4).

Vippagunta teaches that, "It is very important to control the crystal form of the drug during the various drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics." (page 5).

Vippagunta teaches that there are reversible and irreversible polymorphs (page 6), and polymorphs which are structural or conformational polymorphs (pages 7-11). Vippagunta further teaches that, "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case." (page 11).

Vippagunta teaches that "Phase changes due to hydration/dehydration and salvation/desolvation of pharmaceutical compounds during processing or in the final product

may result in an unstable system that would effect the bioavailability of drug from solid dosage forms. Various types of phase changes are possible in solid-state hydrated or solvated systems in response to changes in environmental conditions... For example, some hydrated compounds may convert to an amorphous phase upon dehydration and some may convert from a lower to a higher state of hydration yielding forms with lower solubility. Alternatively, a kinetically favored but thermodynamically unstable form may be converted during pharmaceutical processing to a more stable and less soluble form." (page 17).

Vippagunta teaches that, "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds.... There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates." (page 18).

(5) The relative skill of those in the art:

The relative skill of those in the art is low with regards to determining which solvates of a compound can be formed.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided for salts of the compounds and making them. However, the specification does not provide examples of making solvates.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above and the high unpredictability in the art with regards to solvates and the inability to make generalizations regarding them, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make solvates of the compounds commensurate in scope with the claims.

Claims 35 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated that, "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the

claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated that, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not

constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn generally to solvates of compounds.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is low, particularly with regards to making solvates, as stated above, being that a particular solvate of a compound cannot be predicted.

(2) Partial structure:

The specification and claims provide for the compound in the solvate, however no structure or chemical entity is provided for as being the solvent molecule in the solvate.

(3) Physical and/or chemical properties and (4) Functional characteristics:

The compound must be a solvated compound and comprise a solvent molecule which thus forms the solvate.

(5) Method of making the claimed invention:

Methods of making a particular solvate are unpredictable and the disclosure provide no guidance or examples on which solvates of which compounds can be made, nor does the specification provide guidance as to selection of solvents which will result in solvates of any compound in the specification.

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 35 and 41 is/are broad and generic, with respect to all possible solvate encompassed by the claims. The possible structural variations are limitless to any solvent/solvate molecule. Moreover, the specification is void of any exemplary solvate, and even disclosure of one would not be sufficient to reflect this variance in the genus of solvents that may form a solvate. While having written description of the compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the solvates of compounds as embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 103

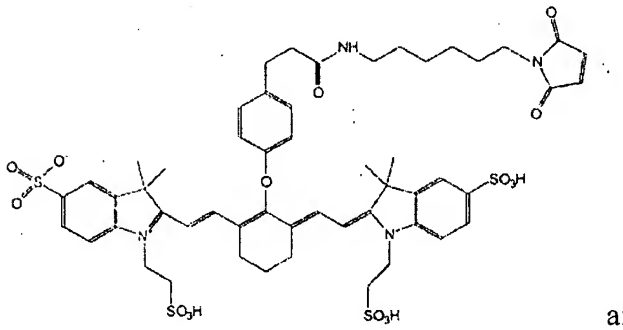
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

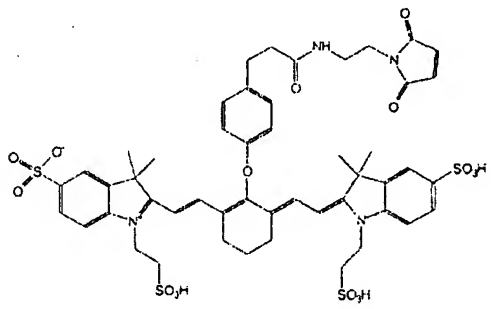
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over ZAHEER in view of ROSENBLATT or CHOREV.

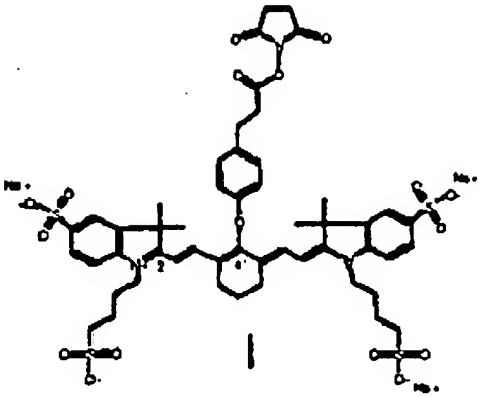
The instant claims are drawn to fluorescent probes with the structures of the two species:

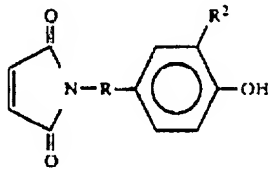
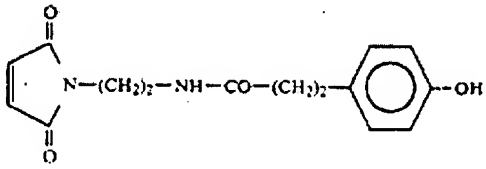


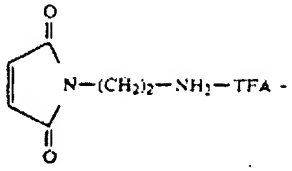
and

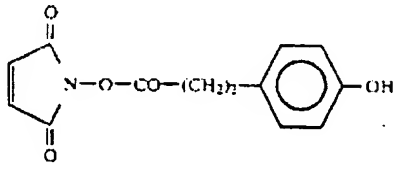
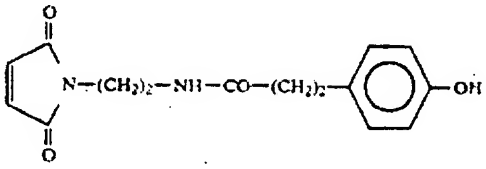


and the genus embracing them.

Zaheer teaches the compound:  (Figure 1, page 357).

Chorev teaches the maleimido ligand generically:  (column 2), where R can be $(CH_2)_n$-NHCO-$(CH_2)_m$ and R^2 can be H, n and m are each 0-2, and further teaches the compound:  (column 3) and the reaction of



VII (column 5) with the succinimidyl ester  to form the compound: 

Chorev additionally teaches that that the maleimido has high specificity towards sulfhydryl and forms a stable thio-ether bond and sulfhydryl has high reactivity towards

maleimido moieties (column 2, lines 12-30). Chorev teaches the reactivity of the maleimido towards sulfhydryl groups (e.g. Chorev at columns 5 and 7) and that it is used for labeling of proteins.

The differences between that which is claimed, and that which is taught in the prior art is that while Zaheer teaches the core structure of the fluorescent dye having propyl sulfonate groups, Zaheer does not teach the instantly claimed linker or ethyl sulfonate groups.

It would have been obvious to one of skill in the art at the time of the invention to have made the compound of Zaheer with the linker of Chorev in order to make a fluorescent compound that was selective towards sulfhydryl groups.

One would have been motivated to make the fluorescent dye with the linker of Chorev in order to make a fluorescent compound which is more selective towards sulfhydryl groups.

One would have a reasonable expectation for success in making the fluorescent compound of Zaheer with the linker of Chorev, as the core structure and synthetic methods of coupling linkers to fluorescent markers are well known to the artisan.

With regards to the length of the alkyl chains in the sulfonate groups, the MPEP states, "A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)." *See* MPEP § 2144.09. Furthermore, MPEP § 2144.09 states in part, "Prior art structures

do not have to be true homologs or isomers to render structurally similar compounds *prima facie* obvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979)". In the instant case, one would have been motivated to make the compounds with varying alkyl chain lengths with the expectation that the compounds having close structural similarities, sharing a core structure. and having the same function (as fluorescent dyes), would have similar properties.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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